

## **Rhinocort Aqua 32 and 64 µg/dose**

*budesonide*

**Nasal spray, suspension**

### **Qualitative and quantitative composition**

One dose (0.05 ml) contains budesonide 32 micrograms or 64 micrograms.

### **Pharmaceutical form**

Nasal spray, suspension.

### **Therapeutic indications**

Seasonal and perennial allergic rhinitis, and vasomotor rhinitis.

Preventively against nasal polyps after polypectomy.

Symptomatic treatment in nasal polyposis.

### **Posology and method of administration**

The posology must be adjusted individually.

#### *Rhinitis*

Adults and children from 6 years of age: The recommended initial dose is 256 micrograms daily. The dose can be administered once daily in the morning, or divided into two administrations, morning and evening. This implies 128 micrograms (2 x 64 micrograms) into each nostril in the morning or 64 micrograms into each nostril morning and evening.

No further effect has been shown for daily doses higher than 256 micrograms.

For elderly patients the posology is the same as for adults.

When the desired effect has been obtained, the dose is reduced to the lowest amount necessary for control of the symptoms. Clinical trials show that a dose of 32 micrograms into each nostril in the morning may be sufficient for some patients.

Symptomatic relief occurs in some patients within only 5-7 hours after the start of treatment. The full effect is only obtained after a few days of treatment (in rare cases not until after 2 weeks). Treatment of seasonal rhinitis should therefore, if possible, start before exposure to the allergens.

In cases of severe nasal congestion the adjunct of a vasoconstrictor may be required.

Supplementary treatment may sometimes be necessary in order to counteract any ocular symptoms caused by the allergy.

#### *Symptomatic treatment and prevention of nasal polyps*

The recommended dose is 256 micrograms daily. The dose can be administered once daily in the morning or divided into two administrations morning and evening. After the desired clinical effect is obtained the maintenance dose should be tapered to the smallest amount necessary to control the symptoms.

*Instructions for correct use of Rhinocort Aqua:*

It is important to instruct the patient to carefully read: “Instructions for use and handling, and disposal”

### **Contraindications**

Earlier hypersensitivity to budesonide or to any of the excipients.

### **Special warnings and special precautions for use**

During long-term treatment with high doses, systemic effects of glucocorticoids such as hypercortisolism, adrenal suppression and/or delayed growth in children can occur. Long-term effects of nasal steroids in children have not been established. Treatment with cortisone-containing medicinal products can lead to slower growth. Regular monitoring of growth is recommended in children and adolescents receiving long-term treatment with corticosteroids, irrespective of the administration form. If delayed growth is suspected, this must be investigated. The benefits of glucocorticosteroid treatment must be placed in relation to possible risks of inhibition of growth.

Caution must be observed when treating patients with nasal fungal or herpes infections.

Caution is necessary in the treatment of patients transferred from systemically acting glucocorticosteroids to Rhinocort Aqua where disturbances in the hypothalamic-pituitary-adrenal axis is suspected. In these patients the dose of systemic steroid should be cautiously reduced, and tests of hypothalamic-pituitary-adrenocortical function should be considered. They may also require the addition of systemic steroids in connection with periods of stress, e.g. surgery, trauma, etc.

Severely reduced liver function affects the pharmacokinetics of orally administered budesonide, resulting in a lower elimination rate and increased systemic availability. Account may need to be taken of possible systemic effects.

Special vigilance may be needed in patients with pulmonary tuberculosis.

Rhinocort Aqua should not come into contact with the eyes. If Rhinocort Aqua comes into contact with the eyes, rinse immediately with water.

Concomitant treatment with ketoconazole or other potent CYP3A4 inhibitors should be avoided. If this is not possible, the interval between administrations of the medications should be as long as possible (see Interactions with other medicinal products and other forms of interaction).

### **Interactions with other medicinal products and other forms of interaction**

Oral ketoconazole 200 mg once daily increased the plasma concentrations of oral budesonide (3 mg in a single dose) on average six-fold when administered simultaneously. When ketoconazole was administered 12 hours after budesonide the concentration increased on average three-fold. Information on this interaction is lacking for nasal budesonide, but greatly increased plasma levels are expected there too. Since there is an absence of data to permit dosage recommendations for nasal administration, the combination should be avoided. If this is not possible, the interval between administration of ketoconazole and budesonide should be as long as possible. A

reduction of the budesonide dose must also be considered. Other potent inhibitors of CYP3A4 probably also cause a marked increase in the plasma levels of budesonide.

## **Pregnancy and lactation**

### *Pregnancy*

Data from more than 2000 pregnancies do not indicate any increased risk of malformations in general for Rhinocort Aqua treatment. Compared to expected incidence, a small increase in the occurrence of minor heart malformations has been detected in children where the mother has been exposed to Rhinocort Aqua in early pregnancy, however a relationship to the exposure is not likely.

During pregnancy, the aim must be the lowest effective dose and the shortest treatment period of Rhinocort Aqua.

### *Lactation*

It is not known whether budesonide passes into human breast-milk. Treatment with Rhinocort Aqua in women who are breastfeeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child.

## **Effects on ability to drive and use machines**

Rhinocort Aqua does not affect ability to drive or use machines.

## **Undesirable effects**

Approx. 5 % of treated patients can be expected to experience side effects in the form of local irritation.

Common (>1/100):    *Airways:* Local irritation, slight haemorrhagic nasal secretion, epistaxis.

Rare (<1/1000):     *General:* Angio-oedema

*Skin:*     Urticaria, rash, dermatitis, pruritus.

*Airways:* Nasal septum perforation, ulceration of mucous membrane.

Immediate or delayed hypersensitivity reactions including urticaria, rash, dermatitis, angioedema and pruritus have been reported.

In very rare cases, ulceration of mucous membrane and nasal septum perforation have occurred with use of nasally applied steroids. The cause of these side effects (the steroid, the underlying disease, or other factors) is not clear.

## **Overdose**

Acute overdose with Rhinocort Aqua, even high doses, is not expected to cause any clinical problems. When Rhinocort Aqua is used chronically in high doses, systemic effects of glucocorticoids such as hypercortisolism and adrenal suppression may occur.

## **Pharmacodynamic properties**

Budesonide is a glucocorticoid with powerful local anti-inflammatory effects.

The exact mechanism of action of glucocorticoids in the treatment of rhinitis is not fully understood. Anti-inflammatory effects such as inhibited release of inflammatory

mediators and inhibition of cytokine-mediated immune response are probably important. The activity of budesonide measured as the affinity for glucocorticoid receptors is approx. 15 times greater than that of prednisolone.

Given prophylactically before nasal provocation, budesonide has been shown to protect against immigration of eosinophils and hyper reactivity.

With recommended doses, Rhinocort Aqua causes no clinically significant changes either in basal plasma cortisol levels or in response to ACTH stimulation. However, dose-related suppression of plasma and urinary cortisol has been observed in healthy volunteers following short-term administration of Rhinocort Aqua.

A dose-response relationship was not found in clinical trials in children with seasonal or perennial allergic rhinitis or in adults with perennial allergic rhinitis.

Vasomotor rhinitis (non-allergic rhinitis) has not been documented with Rhinocort Aqua in the strengths 32 and 64 micrograms/dose.

### **Pharmacokinetic properties**

#### *Absorption*

The systemic availability of budesonide from Rhinocort Aqua is 33 % of the metered dose.

The kinetics are dose-proportional at clinically relevant doses. In adults the peak plasma concentration after administration of 256 micrograms budesonide from Rhinocort Aqua is 0.64 nmol/l, and is reached within 0.7 hours. The AUC (area under the curve) after administration of 256 micrograms budesonide from Rhinocort Aqua is 2.7 nmol x hours/litre in adults and 5.5 nmol x hours/litre in children, which indicates a higher systemic exposure to glucocorticoids in children.

#### *Distribution and metabolism*

Budesonide has a volume of distribution of approx. 3 l/kg. Binding to plasma proteins is 85-90 %. Budesonide undergoes extensive (~90 %) first-passage metabolism in the liver to metabolites with low glucocorticoid activity. The glucocorticoid activity of the principal metabolites, 6- $\beta$ -hydroxybudesonide and 16- $\alpha$ -hydroxyprednisolone, is less than 1 % of that of budesonide. Budesonide does not undergo any local metabolism in the nose.

#### *Elimination*

Budesonide is eliminated by means of metabolism that is catalysed principally by the enzyme CYP3A4. The metabolites are excreted unchanged or in conjugated form, mainly via the kidneys. Only negligible amounts of intact budesonide have been detected in the urine. Budesonide has a high systemic clearance (0.9-1.4 l/min) and the plasma half-life after intravenous administration is on average 2-3 hours.

### **Preclinical safety data**

Conventional studies of general toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction did not reveal any special hazard for humans. In animal reproduction studies, corticosteroids such as budesonide have been shown to induce malformation (cleft palate, skeletal malformations). However, these animal experimental results do not seem to be relevant in humans at the recommended doses of Rhinocort Aqua.

**List of excipients**

Microcrystalline cellulose  
Carboxymethylcellulose sodium  
Anhydrous glucose  
Polysorbate 80  
Disodium edetate  
Potassium sorbate (E 202)  
Hydrochloric acid  
Purified water

The amount of preservative, potassium sorbate (E 202), is 1.2 mg/ml in both strengths.

**Shelf-life**

Please refer to expiry date on the label or outer carton.

**Special precautions for storage**

Do not store above 30 °C.  
Do not freeze.

**Nature and contents of container**

Brown glass bottles fitted with a spray pump and nasal applicator.

**Pack size:**

Please refer to outer carton for pack size.

**Date of revision of text:**

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## **Instructions for use and handling, and disposal**

Read the information before using Rhinocort Aqua nasal spray. Follow the directions carefully.

Before Rhinocort Aqua is used for the first time, the nasal applicator must be loaded with the drug. Shake the bottle, and then spray into the air, until there is an even spray. The effect of this lasts approx. 24 hours. If a longer time elapses before the next dose is taken, the nasal applicator must be loaded with the drug again. This time it is sufficient to spray just once (1) into the air.

- 1 Blow your nose.  
Shake the bottle.  
Remove the brown protective cap. *>Pictures<*
- 2 Hold the bottle as shown in the pictures.
- 3 Insert the tip into your nostril and pump the number of doses prescribed. Administer the spray into the other nostril in the same way.
- 4 Replace the brown protective cap. Do not use Rhinocort Aqua nasal spray more often than prescribed.

### **Children**

Children should only use Rhinocort Aqua nasal spray under supervision by an adult to ensure that the dose is correctly administered and that the dosage is according to the doctor's prescription.

### **Cleaning**

Clean the upper plastic parts regularly. Remove the brown protective cap and lift off the white nasal applicator. Wash the plastic parts in warm water. Allow the plastic part to air-dry completely before replacing them.

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